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REVIEW

Innovative Surgical Approaches That Improve Individual Outcomes in Advanced Breast Cancer

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Abstract: Breast cancer is the most common cause of cancer death in women and the second cause in the general population. The incidence has increased over time. Women in developing countries often present at an advanced stage where initial surgery is not feasible. Short disease-free intervals, the number of metastatic organs and liver metastasis were consistently associated with poor overall survival. Surgery is an integral part of the therapeutic plan for locally advanced breast cancer. The integration of surgical care into the management of patients with advanced cancer has changed substantially with the use of neoadjuvant chemotherapy. Also, more recently, neoadjuvant endocrine therapy and targeted therapies offer new opportunities to downsize the tumor burden and transform the role of surgery for this population from palliation to largely curative intent. Innovative surgical approach to the primary tumor in metastatic disease may provide survival benefits and local control in some patients. Similar to systemic therapy, surgical therapy for secondary dissemination should be considered in certain cases for improved individual outcomes. Advances in reconstructive techniques have improved the quality of life of these patients.

Keywords: breast cancer, locally advanced, metastatic, individual outcomes, surgery

Introduction

According to GLOBOCAN, breast cancer is the most common cancer worldwide – surpassing lung cancer for the first time in 2020 – and the most frequently encountered cancer diagnosed in US women. It is the leading cause of cancer death in less developed countries and the second leading cause of cancer death in American women. In the same year, globally approximately 2.3 million women were diagnosed with breast cancer (11,7% of all sites) and 685,000 deaths were recorded (6.9% of all sites). Breast cancer represents almost 12% of neoplasms found worldwide. Every 14 seconds, somewhere in the world, a woman is diagnosed with breast cancer. Since 2008, the worldwide incidence of pathology has increased by over 20% and mortality by 14%. In 159 out of 185 countries studied, breast cancer represents one in four cases and one in six deaths in female population. The highest incidence was identified in Australia, Western Europe, North America, at the opposite pole being South Central Asia, Central and Eastern Africa. Globally, it is predicted that in 2040 there will be 2,964,197 new cases of female breast cancer.[1] In Romania, breast cancer registers one of the highest death rates, of 17.4% women, 62% more than in Norway, the last ranked, being in the first place among the causes of death by cancer in women and the second place in the general population after the lung cancer. According to the Worldwide Cancer Survival Surveillance Program - CONCORD - it shows that Romania ranks last in the EU, with a 5-year survival rate of 74.9%, almost 20% lower compared to northern and western European countries.[2]

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Table 1 AJCC Clinical Stages IIIA, IIIB and IIIC

Stage	TNM	Explanations
IIIA	T0-3, N2, M0	Some clinicians consider N2 disease as locally advanced whereas T3 N1 is usually not considered as LABC
IIIB	T4, N0-2, M0	T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); inflammatory carcinoma is classified as T4d
IIIC	Any T, N3, M0	N3: Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.

Notes: Adapted from Hortobagyi GN, Connolly JL, D'Orsi CJ et al. Breast. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al, editors. *AJCC Cancer Staging Manual*. 8th ed. Switzerland: Springer International Publishing AG; 2017. p. 589–628. Adapted with permission of SNCSC.[4]
Abbreviations: AJCC, American Joint Committee on Cancer; TNM, tumor, lymph node, metastasis; LABC, locally advanced breast cancer.

Advanced breast cancer is a current health problem due to the diagnosis at this stage of a significant number of cases nowadays. An increased risk for advanced breast tumors is the appearance of ulcers that can become infected very easily due to immunosuppression, which can lead to appearance of sepsis and septic shock.[3] Surgical treatment in such cases no longer corresponds to the standardized indications. Many times we need adjunctive treatment methods to bring the patient to an operable stage or to use innovative methods - such as in the case of metastatic disease.

Discussion

According to the ESMO guidelines, advanced breast cancer is a broader term that includes two entities: locally advanced breast cancer and metastatic breast cancer.

Locally advanced breast cancer (LABC) is defined as cancer without evidence of metastatic disease that cannot be surgically resected without prior systemic therapy or radiotherapy. It is included usually stage IIIB and IIIC, according to the "American Joint Committee on Cancer (AJCC) - Cancer Staging Manual" classification (Table 1),[4] but whereas some clinicians include also patients with IIIA disease.

Metastatic breast cancer includes stage IV with identification of distant metastases (bones, liver, lung, etc).[4,5] At the same time, patients with apparent stage III disease have a sufficiently high incidence of simultaneous distant disease to justify imaging diagnosis. With conventional staging procedures (chest radiography, abdominal ultrasonography, and bone scan), the incidence of simultaneous metastases was >10% and up to 37% if chest and abdominal CT scans were used.[6]

In the decision of treatment of advanced breast cancer, the doctor is obliged to fit the target goals. First, the treatment must be aimed at ensuring radicality. Secondly if radical treatment is impossible, it remains to limit ourselves in improving the quality of life and prolonging survival.

Locally Advanced Breast Cancer

Historically, surgery has been the oldest treatment for breast cancer. With the introduction of the Halstedian mastectomy, this surgery has become a standard in the management of breast cancer with the publication of Halsted's article in 1984. However, long-term results have been poor, with survival ranging from 13 to 20% at 5 years.[7]

After that, the modified radical mastectomy appeared with the Fisher's research in 1985 and it confirmed the similar survival rate results with radical mastectomy in a number of prospective randomized trials.[8]

Management of locally advanced breast cancer is a huge challenge, because of their size, extension to the skin, to the chest wall, and regional lymph node involvement.[9] These patients have a high rate of local recurrences and distant metastases. Therefore, a single surgery brings poor results. The treatment has evolved from a single type of treatment, aggressive surgery or higher doses of radiation in inoperable disease, to multimodal type: neoadjuvant chemotherapy, surgery, radiation therapy, with or without hormonal therapy. Some studies demonstrate that trimodal therapy has proven its superiority over other combinations over time for locoregional control and disease-free survival.[10] However, the optimal sequencing of therapies remains an important topic of future research.

Even if neoadjuvant chemotherapy according to the study does not improve overall survival,[11] its advantage is to change locally advanced breast cancer, previously unresectable, into an operable one. In operable tumors, the advantage is to reduce

the stage and leading to an increase in the percentage of the breast conservation procedure. On the other hand, approximately 10% of patients will choose to perform a mastectomy even if the surgeon recommends breast conservation surgery.[12]

Post-neoadjuvant surgical options include modified radical mastectomy or breast conserving surgery. For most patients with locally advanced breast cancer, mastectomy should be considered the standard of care. Approximately 20–23% of post-neoadjuvant patients are candidates for conservative surgery.[13] It may be considered on a case-by-case basis when the surgeon believes the disease can be completely resected and the patient expresses a strong preference for breast conservation.

The National Comprehensive Cancer Network (NCCN) recommends that initial stage III A/B/C tumors (except T3N1) with good response be treated with mastectomy or be considered for conserving surgery (plus axillary lymphadenectomy and radiotherapy).[14]

The modified radical mastectomy technique is described in the surgery literature. It has not changed substantially over time. The technique of conservative breast surgery with limited indications, as was mentioned, includes quadrantectomy (removal of approximately a quarter of the breast tissue, with 2–3 cm of healthy tissue surrounding the tumour - used less often because of the poorer aesthetic result) and lumpectomy (removes only the tumour mass with a narrow margin of normal tissue).[15]

Toilet Mastectomy

Toilet mastectomy is not widely accepted terminology. It is a palliative procedure for breast cancer that aims to remove breast tissue and skin to minimize local complications. Not being a curative technique the aim is limiting the disease and reducing morbidity. Local complications such as bleeding and secondary infection are most distressful to the patient, because they continue to be a good adjunct to palliative care in advanced breast cancer. This intervention should only be performed if the patient is not eligible for neoadjuvant chemotherapy and would improve his quality of life. Even if the surgical procedure is palliative, good three dimensional margins are important to reduce the occurrence of local recurrences.[16]

Sometimes, when the tumor formation is completely excised, a large defect is created (which does not allow primary wound closure) and reconstruction methods may be required to cover it.

Reconstruction Methods

There are various methods of reconstruction that depend on the extent of the resection, the characteristics of the wound, the associated pathologies of the patient. If the resection of the chest wall is necessary, various synthetic meshes can be used. If the chest wall is not affected, then the skin graft remains an option to be considered. The most common methods to cover large defects use musculocutaneous and fasciocutaneous flaps, most often using the latissimus dorsi muscle, rectus abdominis and external oblique.[17] Although the rectus abdominis flap can cover larger defects, it can be associated with several late complications such as abdominal wall laxity and hernia.[18,19] Although the already mentioned flaps are the first choice for postmastectomy reconstruction, free flaps with microvascular anastomoses can be considered when pedicled ones cannot be performed. They are not commonly used, but sometimes they can become the only reconstruction solution due to their excellent versatility. The tensor fascia lata, rectus femoris, rectus abdominis, remain an option to be considered in those cases with considerable tissue loss. More recently, Deep Inferior Epigastric Perforator (DIEP) flaps have been used with reduced morbidity and reduced impact on adjuvant treatment planning.[20]

Metastatic Breast Cancer

The group of patients newly diagnosed with distant disease at presentation remains approximately 6%, remaining to have a serious prognosis, with a median survival of up to 2 years.[21] While systemic treatment such as chemotherapy, hormonal and biological therapy have become increasingly effective, the survival of women with metastatic disease has continued to improve.

The surgical approach to the primary tumor in the case of metastatic disease is already a well-known idea in oncology. Many of them have shown promising results.[22] There are studies that demonstrate the restoration of immune competence after resection of the primary tumor, making secondary dissemination more vulnerable to systemic therapy.[23]

With the identification of circulating tumor cells in the blood and disseminated tumor cells in the bone marrow of breast cancer patients, the concept of metastasis is a late event.

One thing to note is that the genomic analysis of the metastases and the primary tumor turned out to be different. Because of this, they would likely not respond to the same systemic therapy. This is because excision of the primary formation and focused systemic therapy for metastatic disease potentially directed by its genetic signature.[24]

Although they are not well-designed studies, some retrospective studies support the idea of resection of the primary tumor in patients with a distant disease. An example is Tosselo's meta-analysis which tells us that mastectomy in metastatic disease can be done for increasing the women's survival assuming the risks, benefits and costs together.[25] A study of stage IV breast cancer patients in the National Cancer Data Base (NCDB) of the American College of Surgeons (ACS) evaluated more than 16,000 patients. The 3-year survival for all patients was 24.9%. Median survival for the no-surgery group was 19.3 months, 26.9 months for those undergoing partial mastectomy, and 31.9 months for those undergoing radical mastectomy.[26]

Another study involved 224 patients diagnosed with breast cancer stage IV, some underwent surgery and some did not. The clinical size of the tumor, the number of metastatic sites, the amplification of the HER2 gene were significant predictors of overall survival. There was also a trend toward improved overall survival in those patients who underwent surgical resection.[27]

Another important study that supports the idea of resection is carried out by Gnerlich on a group of over 9000 patients with std cancer. IV. Patients who had surgery were 37% less likely to die during the study period.[28]

Surgery for Metastases

Compared with other metastatic solid tumors, resection of metastases in breast cancer is not a routine procedure. However, as I mentioned before, a more aggressive surgical approach for metastases is required with the increasing in survival due to increasingly efficient systemic therapies.

A 2020 study concluded that liver resection after systemic therapy was associated with a survival advantage over systemic therapy without surgery, particularly in the HER2-positive subtype.[29]

Pulmonary metastases can also be addressed surgically. Friedel's study of 467 patients concluded that due to the low morbidity and mortality rates, pulmonary metastasectomy is now believed to be the best treatment option in selected cases of solitary pulmonary metastases from breast cancer.[30] Brain metastasis is diagnosed in approximately 10% of patients with breast cancer std. IV and radiosurgery has survival advantages over whole skull radiation therapy.

New Research Directions

Medicine is in a continuous development, because of this new directions of research are necessary to be in trend with the modern discoveries in the field of interest. One of the examples could be the integration of Predictive, Preventive, and Personalized Medicine (PPPM/3PM) in the care of breast cancer. A study by Huang that describes for the first time the marker "m7G" in pan-cancer development as an innovative biomarker in predicting clinical and post-immunotherapy outcomes. But the most appreciated advantage is that of profound integration with predictive, preventive, and personalized medicine offering an exclusive occasion for clinical intelligence and new approaches.[31] Another study by Hon-Yi Shi try to integrate Predictive, Preventive, and Personalized Medicine in the follow-up and treatment of patients with breast cancer. The study follows trends for 10 years and draws conclusions on the quality of life and the cost effectiveness of different surgical approaches for patients with breast cancer.[32]

Conclusion

Although the local symptoms of breast cancer can be devastating, we have many reconstructive options available to us with the use of both pedicled and free flaps, which can facilitate a definitive palliative oncological excision, regardless of the degree of excision required. Treatment planning between the surgical and reconstructive oncology teams is essential for a good outcome and will allow selection of the most appropriate surgical approach.

Most studies have provided important data that local surgical excision for the primary tumor site can allow prolonged survival. Systemic treatments are improving day by day, and a complete clinical response for metastatic disease is not an exception. So, it is important to accept the idea that surgical resection of all primary locoregional tumors could limit the local or systemic recurrence.

The results of the studies suggest that, similar to systemic therapy, surgical therapy for secondary dissemination should be considered in certain cases. The Predictive, Preventive, and Personalized Medicine can be integrated in the

care of patients with breast cancer through future studies to explore its potential. In this way we can be more cost effective, we can optimize the patient's outcomes and increase his quality of life.

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